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Islet-cell antibodies as predictors of the later development of Type 1 (insulin-dependent) diabetes

A study in identical twins

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Summary. To determine the value of islet-cell antibodies, both complement-fixing and non-complement-fixing, in predicting the later development of Type 1 (insulin-dependent) diabetes, we studied different groups of identical twins. Twelve twins have developed diabetes and 11 of these had non-complement-fixing islet-cell antibodies before diagnosis, and eight out of nine tested had complement-fixing islet-cell antibodies. Of the twins who have remained non-diabetic for many years and are now unlikely to develop diabetes, twelve have had non-complement-fixing islet-cell antibodies at some stage but only four have ever had complement-fixing antibodies. In 29 non-diabetic co-twins tested within 5 years of the diagnosis of diabetes in the affected twin the presence of islet-cell antibodies, especially complement-fixing, predicted the progression to frank diabetes with a high specificity (100%), sensitivity (88%) and predictive value (100%). In pairs remaining discordant the antibodies were found more frequently in the diabetic than the non-diabetic twin. We conclude that the presence of islet-cell antibodies is not genetically determined and can occur without progression to diabetes. However, the presence of islet-cell antibodies, especially complement-fixing, in non-diabetic twins tested soon after the diagnosis of their co-twin, indicates a high risk for the development of diabetes.

Key words: Identical twins, islet-cell antibodies, Type 1, (insulin-dependent) diabetes.

The development of Type 1 (insulin-dependent) diabetes is thought to be due to a process of immune-mediated B-cell destruction in genetically susceptible individuals [1, 2]. Non-complement-fixing islet-cell antibodies (ICA-IgG) are detected in the majority of Type 1 diabetic patients tested soon after diagnosis [3] and have also been found in individuals before diagnosis, suggesting that their presence might predict the later development of Type 1 diabetes [4, 5].

Family studies have shown that the majority of first degree relatives who became diabetic had ICA-IgG detectable before diagnosis [6–9]. However, the same prospective studies show that the majority of relatives with these antibodies still remain unaffected [7, 9, 10] indicating that ICA-IgG may not be a highly predictive marker for the development of Type 1 diabetes.

Islet cell antibodies can fix complement (CF-ICA) and the presence of this antibody in non-diabetic subjects may be a better predictor of those likely to become diabetic [11, 12].

Genetic factors may be important in determining the expression of islet-cell antibodies. In diabetic patients the persistence of islet-cell antibodies has been associated with particular HLA antigens [13] and similar results have been reported in non-diabetic relatives positive for islet-cell antibodies [9, 14]. It therefore remains possible that the presence of islet-cell antibodies in the unaffected relatives of Type 1 diabetic patients is due to the sharing of part of the genome rather than reflecting islet-cell damage.

We have tried to distinguish between these possibilities by testing for islet-cell antibodies in unaffected identical twins of Type 1 diabetic patients. If islet-cell antibodies are a marker of islet-cell destruction they should occur more frequently in those twins who later became diabetic. If, however, their presence merely reflects a shared genetic predisposition they should be detected with an equal frequency in both the diabetic and the non-diabetic twins.

Subjects and methods

Details of the ascertainment and proof of identity of the twins included in this study have been previously published [15].

For the purposes of this study we have selected four groups of twins (some twins are included in more than one group).

Group 1: Twelve individual twins who since 1974 have been tested for islet-cell antibodies and, having originally had a normal fasting glucose, have developed Type 1 diabetes.

Group 2: Twelve individual twins who remain non-diabetic but who at some time have been positive for islet-cell antibodies.

Group 3: To assess the sensitivity, specificity and positive predictive value of islet-cell antibodies as markers for the later development of Type 1 diabetes we studied 29 originally non-diabetic twins.

For this analysis we want to be able to detect all the twins who have had islet-cell antibodies but ensure a sufficient period of observation so that those who are going to develop diabetes have done so and the chance of the non-diabetic twins developing diabetes is small. Since the majority of pairs become concordant within 5 years of the diagnosis of diabetes in the co-twin [16] we therefore chose to include all the twins who have been tested within 5 years of the diagnosis of their co-twin and in whom the non-diabetic twins have been observed to achieve a period of discordance of at least five years. Ten of these twins have become diabetic and are also included in Group 1. Two of the non-diabetic twins are also included in Group 2.

Group 4: Sixteen pairs of twins discordant for Type 1 diabetes.

To assess the importance of genetic factors in determining the expression of islet-cell antibodies we studied pairs of twins to examine for differences in the presence of antibodies between the diabetic and non-diabetic twin of each pair. Sixteen pairs were included in whom both twins were tested within 5 years of the diagnosis of the diabetic twin and where the co-twin has not become diabetic after a period of discordance of at least 5 years. The 16 non-diabetic twins from these pairs are also included in Group 3.

In all cases, when non-diabetic, each twin had a normal fasting or post-prandial blood glucose and a normal Hb_{A1} (measured using an electroendosmotic method, Corning, Halstead, Essex, UK).

Methods

For the determination of islet-cell antibodies (ICA-IgG and CF-ICA) sera were tested, undiluted, by indirect immunofluorescence (IFL) on sections of blood group 0 cryofixed human pancreas employing the methods previously described [11, 17] and according to the standard protocol recommended at the First International Workshop for the standardisation of ICA [18].

To facilitate comparison all results are expressed using a visual scale of; very weak positive (vw+), weak positive (w+), positive (+) and strongly positive (++). Since serum is no longer available from the twins it is not possible to express the results in Juvenile Diabetes Foundation (JDF) units. However, 47 later samples from this study were also subjected to end-point titration with doubling dilutions of sera, a single pancreatic substrate and fluoresceinated rabbit anti-human IgG and C3 (Dakopatts, Glostrup, Denmark) for ICA-IgG and CF-ICA determinants respectively. In the latter assay fresh normal human serum was employed as a source of complement. Median titres for those samples scored as vw+, w+, + and ++ were $^1/_2$, $^1/_{16}$, $^1/_{64}$ and $^1/_{256}$ respectively for ICA-IgG and neat, $^1/_2$, $^1/_8$ and $^1/_{16}$ respectively for CF-ICA. For comparison, the 80 unit JDF reference serum gave end-point titres of $^1/_{32}$ for ICA-IgG and $^1/_8$ for CF-ICA when tested blind in each of 2 serum exchanges held during the 2nd Workshop on the Standardisation of ICA [19].

To quantify the sensitivity, specificity and positive predictive value of islet-cell antibodies, analysis was carried out in relation to the number of tests performed. Sensitivity is defined as the percentage of twins who have developed diabetes in whom the test was positive. Specificity is defined as the percentage without diabetes correctly identified by a negative test. Predictive value is the likelihood that a twin with a positive test will develop diabetes [20].

Statistical analysis

Statistical analysis was performed using Fisher's exact test (one-tailed).

Results

Group 1, twins who have developed diabetes

The results of (ICA-IgG) in twins who have developed diabetes are shown in Figure 1. In eleven of the twelve twins ICA-IgG was detected before diabetes was diagnosed, when they had a normal fasting glucose value. The only twin who did not show ICA-IgG (no. 10) was tested only once in 1974, 11 years before she developed diabetes. One twin, (no. 3), was first tested in 1973 and remained positive until diagnosis in 1986, 13 years later.

The results for CF-ICA in the same group of twins are shown in Figure 2. Three twins were not tested before diagnosis: eight of the nine others had CF-ICA before the diagnosis of diabetes. Twin no. 3 was also persistently positive for CF-ICA, albeit at a low level, from 1973 until diagnosis in 1986.

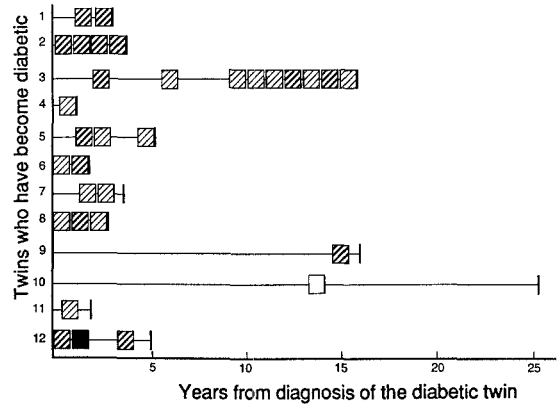

Fig. 1. Non-complement-fixing islet-cell antibodies (ICA-IgG) in twelve twins who developed Type 1 (insulin-dependent) diabetes. Each box represents one test. ■ corresponds to a visual score of strongly positive ++; ▨ to a score of positive +; ▨ to a score of weak positive +; ⊠ to a score of very weak positive vw+; □ indicates that ICA was absent; — indicates not tested; ⊣ refers to the time of diagnosis

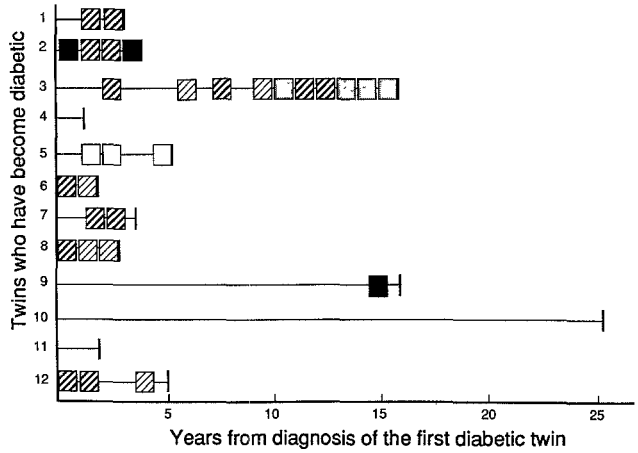

Fig. 2. Complement-fixing islet-cell antibodies (CF-ICA) in twelve twins who developed Type 1 diabetes. The symbols are the same as Fig. 1

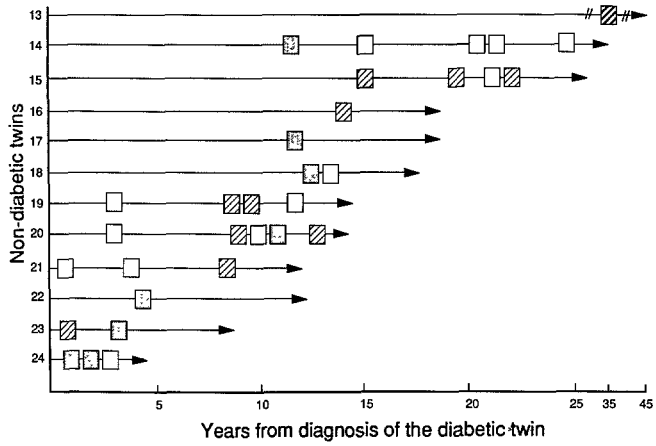

Fig. 3. Non-complement-fixing islet-cell antibodies (ICA-IgG) in twelve twins who remain non-diabetic. The symbols are the same as Fig. 1

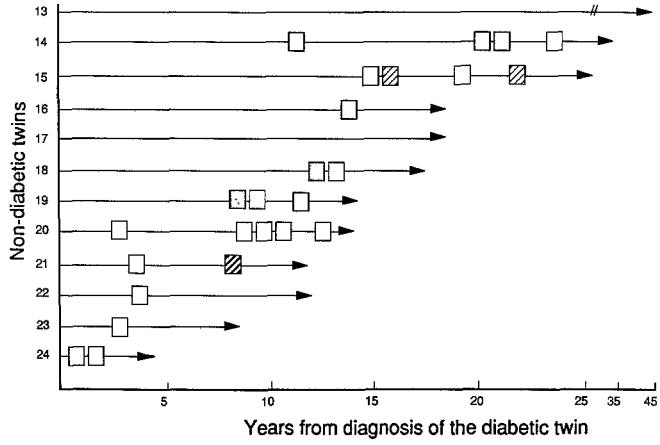

Fig. 4. Complement-fixing islet-cell antibodies (CF-ICA) in twelve twins who remain non-diabetic. The symbol are the same as Fig. 1

Comparing the results for ICA-IgG (Fig. 1) and CF-ICA (Fig. 2), ICA-IgG was generally present at a higher titre and serial sampling showed that in none of the twins did either antibody become undetectable before the diagnosis of diabetes.

Group 2, twins who have had islet-cell antibodies but remain non-diabetic

The results for both ICA-IgG and CF-ICA in twins who have had islet-cell antibodies and who remain non-diabetic are shown in Figures 3 and 4. Four twins were positive for ICA-IgG but have subsequently become negative (nos. 14, 18, 19 and 24). Two of these twins (nos. 18 and 19) had CF-ICA. Two twins have been positive for ICA-IgG and remain so at the time of latest testing (nos. 15 and 23) but only one of these (no. 15) has ever been positive for CF-ICA. Two twins (nos. 20 and 21) have developed ICA-IgG but only one also showed CF-ICA (no. 21). The other four twins have only been tested on one occasion, all had ICA-IgG but only two were also tested for CF-ICA which was absent.

Comparison between the results of islet-cell antibodies in twins from Group 1 (Figs. 1 and 2) with those from twins from Group 2 (Figs. 3 and 4) indicate that in twins who have become diabetic islet-cell antibodies were persistent and generally present at a higher level.

Group 3, predictive value of islet-cell antibodies in twins

Of the 29 twins who were not diabetic when they were tested within 5 years of the diagnosis of their diabetic co-twin, 10 have subsequently developed diabetes. The other 19 have still not developed diabetes, now more than 5 years from the diagnosis in the diabetic twin and are, therefore, less likely to ever become so. The sensitivity, specificity and positive predictive value for the development of diabetes for each antibody is shown in Table 1. Of the 10 twins who have become diabetic all had ICA-IgG and of the eight tested for CF-ICA seven were positive giving a sensitivity of 100% and 88%, respectively. Of the 19 non-diabetic twins 16 did not have ICA-IgG and none of the 15 tested for CF-ICA were positive resulting in a specificity of 84% and 100%, respectively. Thus, of the 13 twins with ICA-IgG 10 have already developed diabetes; all seven twins with CF-ICA have become diabetic giving a positive predictive value of 77% and 100%, respectively.

Group 4, islet-cell antibodies in discordant pairs of twins

Sixteen pairs of twins were tested for ICA-IgG within 5 years of the diagnosis of the diabetic twin. Nine of the diabetic twins had this antibody compared to only three of the non-diabetic co-twins ($p = 0.028$). In only 13 of these pairs were both twins tested for CF-ICA which was found in five of the diabetic but none of the non-diabetic twins ($p = 0.019$).

Discussion

The results in the twins who have developed diabetes are similar to those from prospective family studies showing islet-cell antibodies to be present months or years before the development of frank diabetes [6, 13, 21]. The presence of antibodies for 13 years before the diagnosis in one of the twins (no. 3) is, we believe, the longest period recorded. This study, therefore, adds further support to the view that immune changes can be

Table 1. The sensitivity, specificity and positive predictive value of islet cell antibodies, both non-complement-fixing (ICA-IgG) and complement-fixing (CF-ICA) as a marker for the development of Type 1 (insulin-dependent) diabetes in unaffected identical twins

	ICA-IgG	CF-ICA
Sensitivity	10/10 (100%)	7/8 (88%)
Specificity	16/19 (84%)	15/15 (100%)
Positive predictive value	10/13 (77%)	7/7 (100%)

detected before diagnosis and the progression to hyperglycaemia may be slow [6].

One of the questions this study was designed to answer was whether the presence of islet-cell antibodies indicated an increased susceptibility towards developing diabetes. The finding of a significantly higher prevalence of antibodies in the diabetic than the non-diabetic co-twins suggests that their presence cannot be explained by genetic factors alone.

The calculated specificity and sensitivity of ICA-IgG and CF-ICA in predicting the later development of diabetes can be only an estimate as some of the twins may yet develop diabetes. The sensitivity of both tests was high. All ten of the twins from Group 3 who developed Type 1 diabetes had ICA-IgG and eleven of the twelve twins from the whole study had this antibody detectable before diagnosis. The only exception was tested 11 years before the diagnosis and it is possible that she developed antibodies in the interim. Seven of the eight twins from Group 3 tested for CF-ICA had this antibody before diagnosis. The specificity and positive predictive value was also high for both tests but slightly better for CF-ICA which was rarely found in the non-diabetic twins and none from Group 3.

Twelve twins have, or had, ICA-IgG and remain non-diabetic subjects. The majority of pairs becoming concordant do so within 5 years of the diagnosis in the diabetic twin. We estimate that the chances of a twin becoming diabetic after more than 11 years discordance is less than 3% [16]. In view of the long periods of discordance in these twins, (mean duration of discordance is 19 years and only two twins have been discordant for less than 11 years), it is unlikely that many of these twins who have had islet-cell antibodies will develop diabetes. Thus, islet-cell antibodies can occur in identical twins who are not going to develop Type 1 diabetes.

The apparent superiority of CF-ICA compared to ICA-IgG in predicting the later development of diabetes is in agreement with other studies on high-risk individuals [7, 12]. It remains unclear whether this is because the presence of CF-ICA is more specific of islet-cell damage or merely reflects an increase in the titre of ICA-IgG [22]. Since many of the tests could not be repeated and a titre obtained, this study cannot resolve the question but those twins who have developed diabetes usually had higher levels of ICA-IgG and higher levels of CF-ICA than those who remain non-diabetic.

Fluctuation was detected in some of the non-diabetic twins, a similar finding to that reported from the Barts/Windsor study [23]. Such fluctuation was not seen in any of the twins who became diabetic patients, even twin no. 3 who had a 13 year latent period. This suggests that in addition to the titre the persistence of the antibodies may be an important predictor, perhaps more important than the period of discordance.

The results of the islet-cell antibodies in the twins who remain non-diabetic differ slightly from a previous publication [24]. This is because we have excluded three non-diabetic twins who were erroneously classified as having CF-ICA but this does not alter the fact that islet-cell antibodies can occur in long-standing discordant twins who are unlikely to develop diabetes. The results in the twins are therefore still, apparently, at variance with the reports from a similar cohort tested at the Joslin Clinic [25, 26]. It is probable that much of the apparent discrepency is due to a difference in the sensitivity of the assays. The twins in our study who developed diabetes had higher levels of ICA-IgG and had CF-ICA. The workers at the Joslin claim that their Protein A assay for ICA-IgG will detect those with CF-ICA [27] but in the majority of twins who remain non-diabetic ICA-IgG was detected at low levels without persistent CF-ICA and it is probable that they would not have been detected in the Protein A assay. International standardization may resolve this problem but obviously such comparison of methods cannot be applied to retrospective data such as that in this twin study.

The low levels of antibodies are unlikely to be artefacts. These results can be seen in conjunction with those of activated T-lymphocytes [28] and insulin antibodies [29]. These immune changes are seen in the newly diagnosed Type 1 diabetic twins, but they are also seen in their non-diabetic co-twins even many years after the diagnosis of the diabetic twin when the chances of their developing diabetes are small. The most likely explanation of these observations is that the non-diabetic co-twins are subject to immune-mediated B-cell damage that does not necessarily progress to diabetes [30, 31]. This explanation is supported by the findings of diminished insulin secretion in HLA identical siblings studied many years after the diagnosis of diabetes in their sibling [32]. Furthermore, siblings with ICA, irrespective of HLA status or duration from the diagnosis of their diabetic sibling, show impaired glucose potentiation of the insulin response to arginine [33]. Such a defect is the first abnormality in islet-cell function detectable in baboons gradually rendered diabetic by the sequential administration of streptozotocin [34]. The pathogenesis of Type 1 diabetes has been depicted as a series of stages with progression from the genetic predisposition, through immune-mediated B-cell damage before the eventual development of hyperglycaemia [26]. Although the results of this study and the others cited above do not challenge the theory they do cast doubts about the frequency of the progression to clinical diabetes.

We conclude that immune changes including islet-cell antibodies can occur in non-diabetic twins and do not inevitably lead to diabetes [24]. However, the presence of ICA-IgG in a high titre, especially in conjunction with CF-ICA, appears to indicate individuals at great risk of irreversible B-cell damage.

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